Pauci immune crescentic (necrotizing) GN

By

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vasculitis
MORE COMMON
THAN YOU THINK
MORE SERIOUS
THAN YOU KNOW
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2014
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What is the vasculitis?

Vasculitis is a clinopathological process characterized by inflammation, leucocyte infiltration and necrosis of the blood vessel wall with associated damage of the affected organ e.g. skin, lung, kidney, heart, brain, spleen, liver, GIT. (Multisystem affection + end-organ damage + constitutional manifestations).

Table 2. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

- **Large vessel vasculitis (LVV)**
  - Takayasu arteritis (TAK)
  - Giant cell arteritis (GCA)
- **Medium vessel vasculitis (MVV)**
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- **Small vessel vasculitis (SVV)**
  - Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
    - Microscopic polyangiitis (MPA)
    - Granulomatosis with polyangiitis (Wegener's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Anti–glomerular basement membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- **Variable vessel vasculitis (VVV)**
  - Behçet's disease (BD)
  - Cogan's syndrome (CS)
- **Single-organ vasculitis (SOV)**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- **Vasculitis associated with systemic disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- **Vasculitis associated with probable etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Diagnostic approach

1. **Suspect the disease.**
2. **Exclude underlying cause (secondary vasculitis).**
3. **Rule out vasculitis mimickers.**
4. **Define the type and extent of the disease organ affected) , stage of the disease(activity, chronicity).**
5. **Confirm the diagnosis: investigations**

1- Is it Vasculitis ?

2- Which type ?

3- Pauci-immune?

Is it Vasculitis ?

1

Constitutional symptoms

Fever , headache, anorexia, wt loss, fatigue, arthralgia, myalgia.

2

Multisystem affection

Renal, Lung, Heart, GIT, dermal CNS.

3 - Skin Rash

Non-pruritic palpable purpura.

Is it Vasculitis ?

Multisystem affection

2

Multisystem affection

Renal, lung, heart.

GIT, dermal, CNS.

Basically, vasculitis should be considered in any unidentified multisystem disorder.

Is it Vasculitis ?

Multisystem affection

Upper respiratory tract

- Sinusitis. rhinitis
- Subglotic stenosis.
- Nasal septal collapse
- Tracheal inflammation
- Otitis media,
- Ocular inflammation.

Lungs

- Pulmonary haemorrhage, hemorrhagic alveolar capillaritis
- Necrotizing granulomatous inflammation, nodules cavitations

Is it Vasculitis ?

Multisystem affection

Heart

- Transient heart block, hypokinesis
- Infarction
- Life-threatening myocarditis
- Pericarditis
- Endocarditis

Neurological

- Mononeuritis multiplex.
- Cerebral vasculitis
- Cerebral infarctions

Is it Vasculitis ?

Multisystem affection

GIT

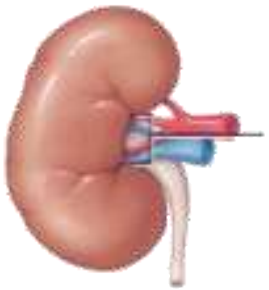
- Mesenteric ischemia: abdominal pain and blood in the stool, rarely intestinal perforation.
- Pancreatitis
- Hepatitis

Is it Vasculitis ?

Multisystem affection

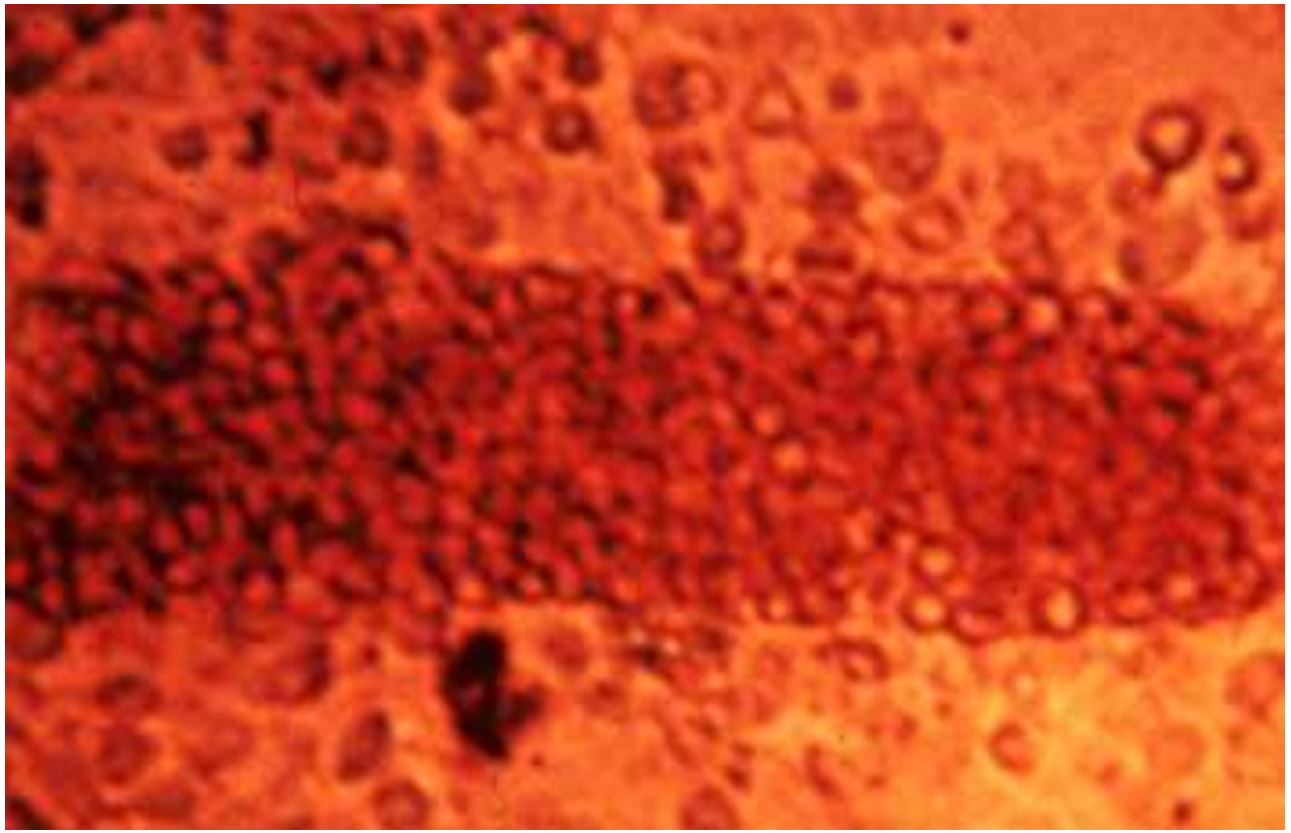
Kidney

- Acute nephritis (active urine sediment)
- RPGN (rapid loss of renal function)
- Subacute or chronic nephritis
- Nephrotic syndrome



Is it Vasculitis ?

Multisystem affection



Red cell casts are specific for glomerulonephritis

Is it Vasculitis ?

Skin

Skin

- Purpura
- Small areas of ulceration
- Red or purple spots
- Itching & rash

Is it Vasculitis ?

Skin

Extremitis

- Ischaemia
- Rash
- Colour changes

Figure 25-4 Cutaneous vasculitis. Ankle of a patient with small-vessel vasculitis, showing purpura and a few small ulcers.

Rash of systemic vasculitis (Palpable purpura)

Livedo reticularis

Fig 1. Livedo reticularis: pink-blue mottling


Punched out ulcers

Digital infarction

Palpable purpura due to small vessel cutaneous vasculitis in a patient with cryoglobulinaemia.

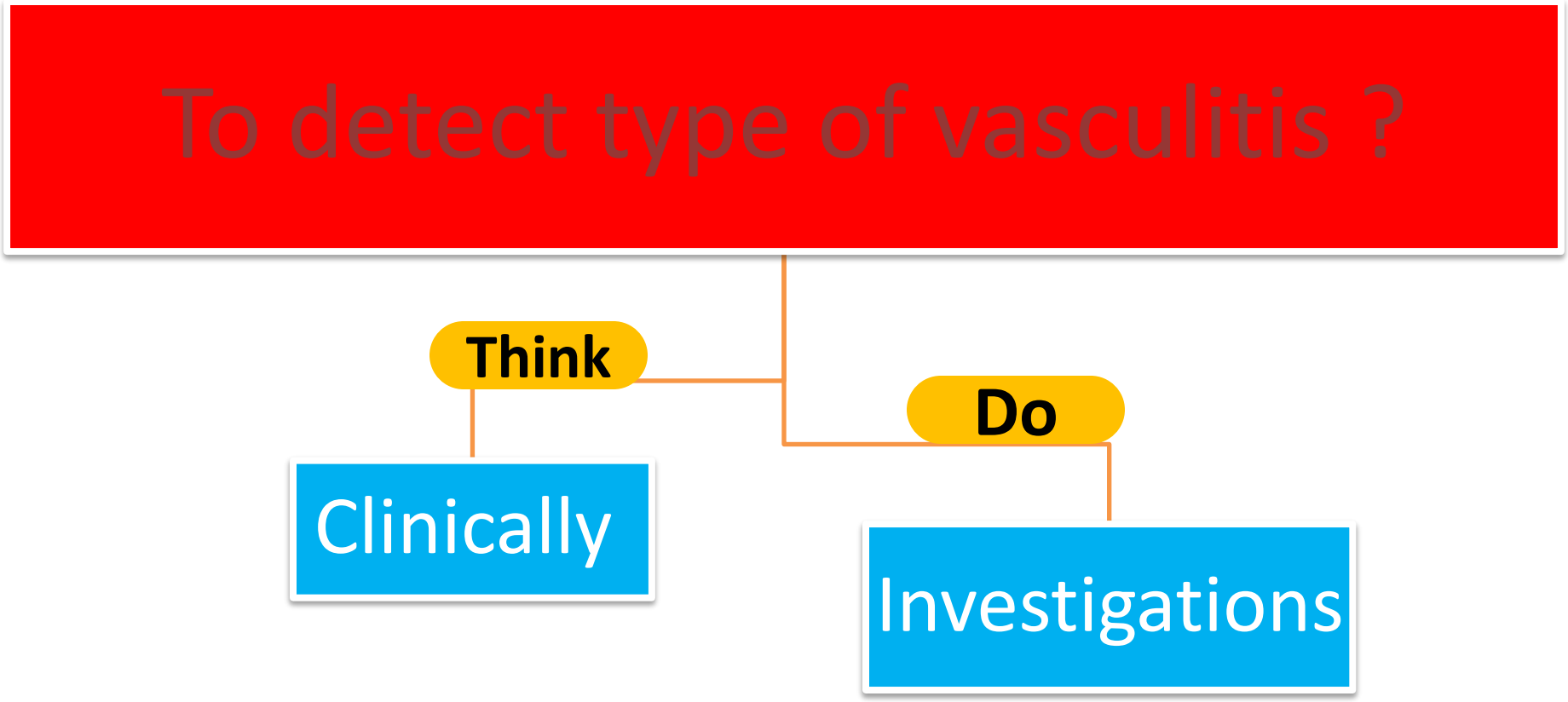
2-Which type ?

1- Is it Vasculitis ?

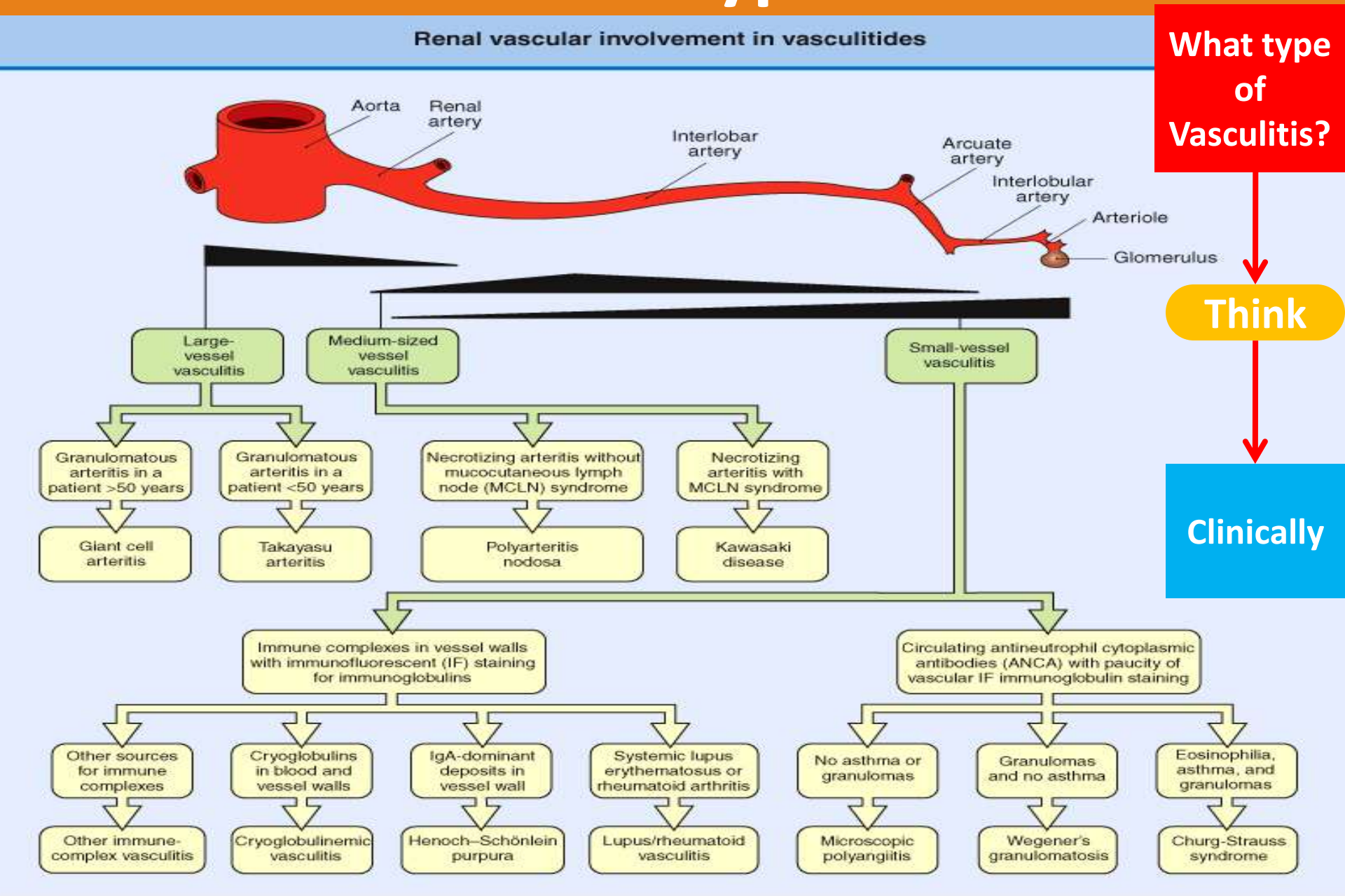
2- Which type ?

3- Pauci-immune?

Which type ?


To detect type of vasculitis ?
Think
Do
Clinically
Investigations

Which type ?



What type of Vasculitis?

Think

Clinically

(Adapted from Jennette JC, Falk RJ: Renal involvement in systemic vasculitis. In Greenberg A, Cheung AK, Coffman TM, et al, eds. National Kidney Foundation nephrology primer, 4th ed. Philadelphia: WB Saunders, 2005, pp 226–233.)

Which type ?

Investigations

What type of Vasculitis?

Do

Investig.

Laboratory:

- **Inflammation:** elevated ESR, CRP, raised WCC with neutrophil leukocytosis, eosinophilia& anemia.
- **Serology:** ANCA, ANA, complement(C3, C4), anti GBM, Rh factor, Immunoglobulin electrophoresis. Anti-dsDNA, ENAs.
- **Renal involvement:** impaired RFT, proteinuria, haematuria, RBC-casts, active urinary deposit.

Which type ?

Investigation

What type of Vasculitis?

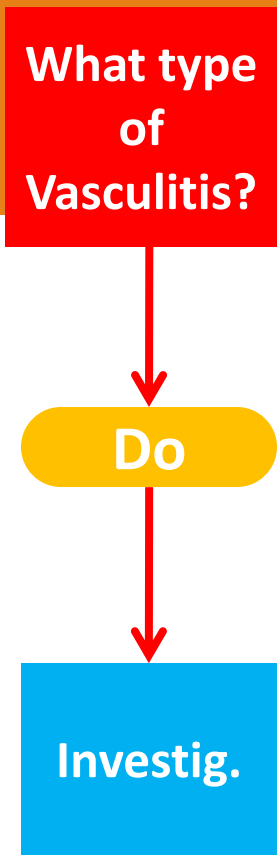
Do

Investig.

Imaging:

- ❑ Renal US
- ❑ CXR
- ❑ CT and MRI skull and nasal sinus
- ❑ Echocardiography

Which type ?



Investigations

Histology and immunohistology

- Biopsy: renal, dermal, temporal artery
- Examination by LM, EM, IF and special stain if indicated.

2-Which type ?

1- Is it Vasculitis ?

2- Which type ?

3- Pauci-immune?

Which type ?

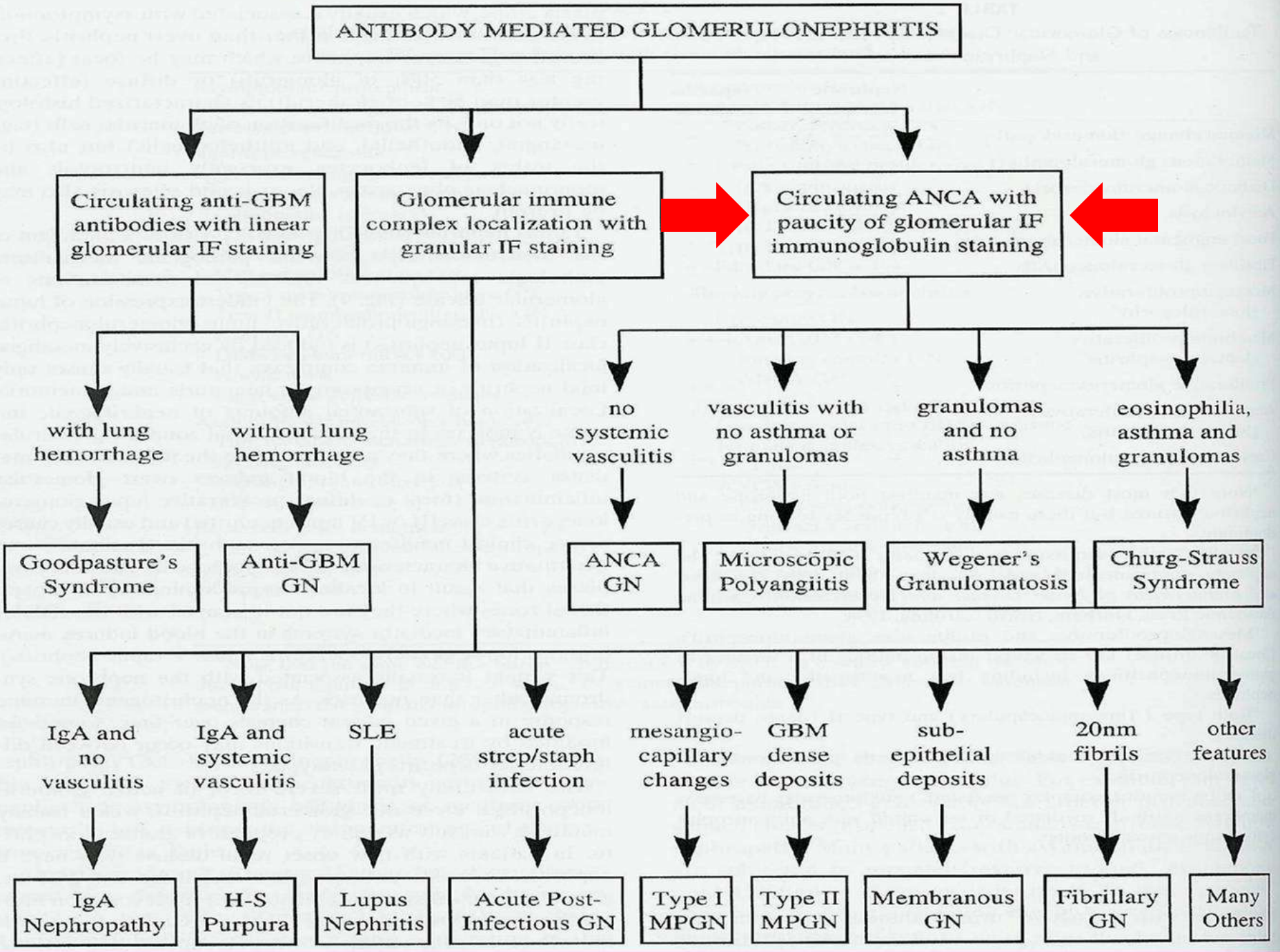
+Ve clinical picture of Vasculitis

+

+Ve ANCA

+

Pauci-immune


ANTIBODY MEDIATED GLOMERULONEPHRITIS
Circulating anti-GBM antibodies with linear glomerular IF staining
Glomerular immune complex localization with granular IF staining
Circulating ANCA with paucity of glomerular IF immunoglobulin staining
with lung hemorrhage
without lung hemorrhage
no systemic vasculitis
vasculitis with no asthma or granulomas
granulomas and no asthma
eosinophilia, asthma and granulomas
Goodpasture's Syndrome
Anti-GBM GN
ANCA GN
Microscopic Polyangiitis
Wegener's Granulomatosis
Churg-Strauss Syndrome
IgA and no vasculitis
IgA and systemic vasculitis
SLE
acute strep/staph infection
mesangio-capillary changes
GBM dense deposits
sub-epithelial deposits
20nm fibrils
other features
IgA Nephropathy
H-S Purpura
Lupus Nephritis
Acute Post-Infectious GN
Type I MPGN
Type II MPGN
Membranous GN
Fibrillary GN
Many Others

Pauci-immune vasculitis ?

Pauci-immune vasculitis is small-vessel vasculitis with pathological glomerular lesion characterized by:

1. Segmental fibrinoid necrosis of the blood vessel (necrotizing small-vessel vasculitis) + crescent formation.
2. Paucity (no or few) of glomerular staining for immunoglobuli by immunofluorescence microscopy (pauci-immune glomerulonephritis).

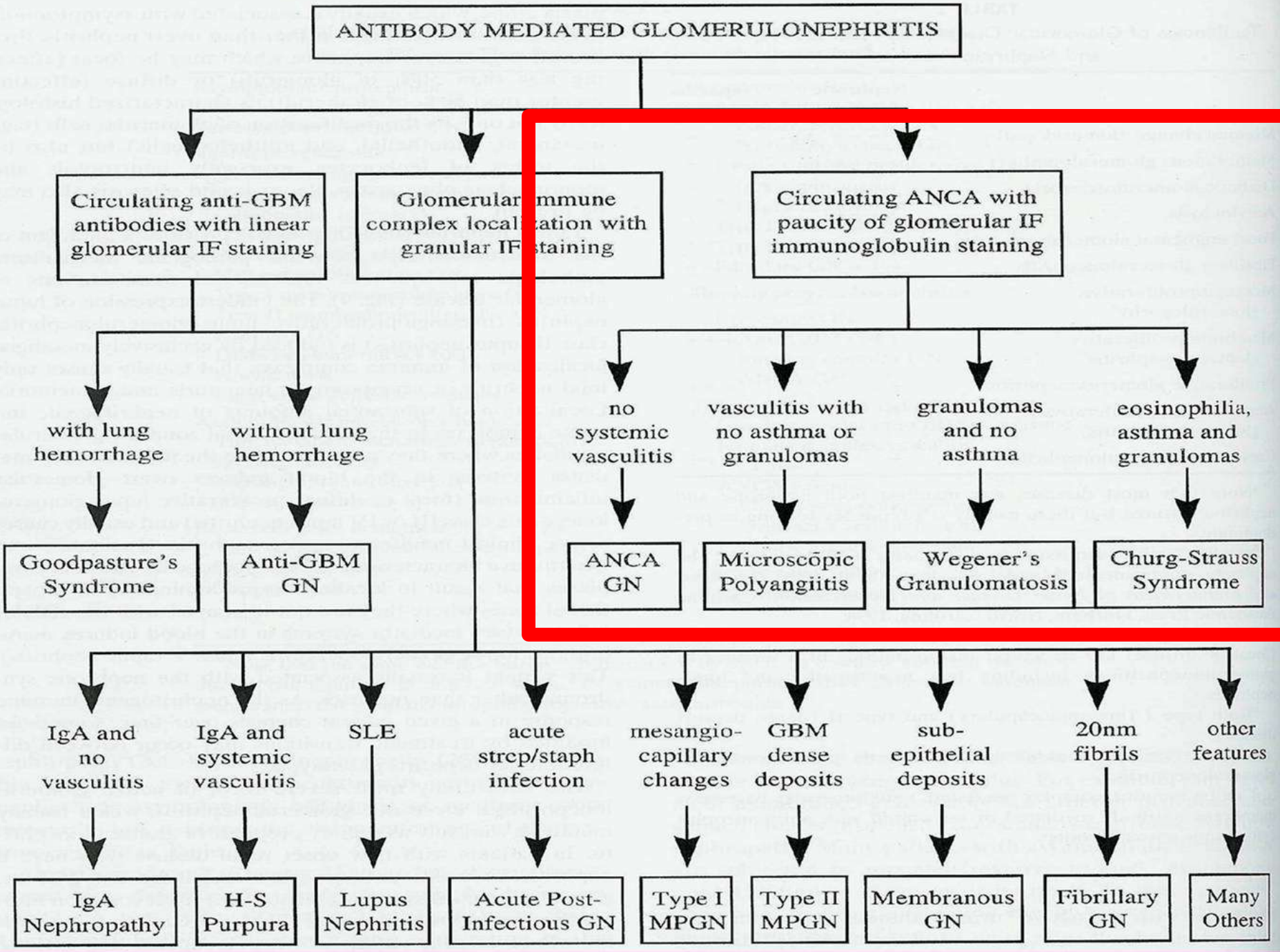
Pauci-immune vasculitis ?

- Small vessels refers to the distal intraparenchymal arterial branches (small arteries that connect with arterioles e.g. renal arcuate and interlobular arteries), as well as arterioles, capillaries, (in glomeruli and pulmonary alveoli) and venules (dermis) and may be veins.

Pauci-immune vasculitis ?

Classification

- Primary (renal-limited) vasculitis (RLV): absence of systemic vasculitis.
- Microscopic polyangiitis (MPA) : absence of evidence of necrotizing granulomatous inflammation.
- Granulomatosis with polyangiitis (Wegener) (GPA) :necrotizing granulomatous inflammation, most often affecting the respiratory tract.
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) : necrotizing granulomatous inflammation. asthma, eosinophilia,


ANTIBODY MEDIATED GLOMERULONEPHRITIS
Circulating anti-GBM antibodies with linear glomerular IF staining
Glomerular immune complex localization with granular IF staining
Circulating ANCA with paucity of glomerular IF immunoglobulin staining
with lung hemorrhage
without lung hemorrhage
no systemic vasculitis
vasculitis with no asthma or granulomas
granulomas and no asthma
eosinophilia, asthma and granulomas
Goodpasture's Syndrome
Anti-GBM GN
ANCA GN
Microscopic Polyangiitis
Wegener's Granulomatosis
Churg-Strauss Syndrome
IgA and no vasculitis
IgA and systemic vasculitis
SLE
acute strep/staph infection
mesangio-capillary changes
GBM dense deposits
sub-epithelial deposits
20nm fibrils
other features
IgA Nephropathy
H-S Purpura
Lupus Nephritis
Acute Post-Infectious GN
Type I MPGN
Type II MPGN
Membranous GN
Fibrillary GN
Many Others

Pauci-immune vasculitis ?

Why pauci-immune vasculitis is grouped together?

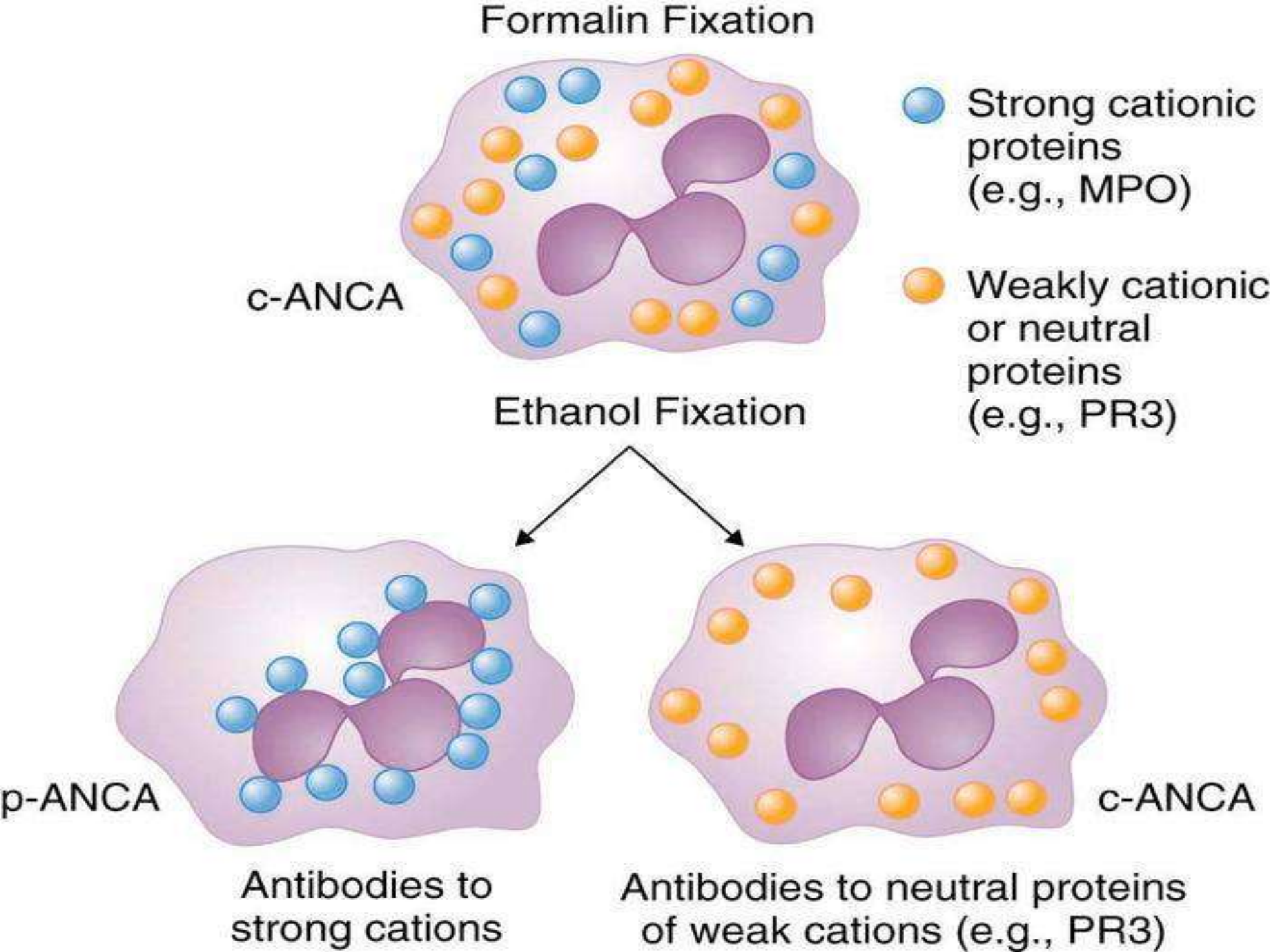
Sharing common characteristics

- Serological: ANCAs-associated.
- Histological: necrotizing small-vessel vasculitis that affects capillaries, venules, arterioles, and small arteries +crescent formation
- Immnohistologic: absence or paucity of Ig deposition (pauci-immune)
- Their treatment is identical

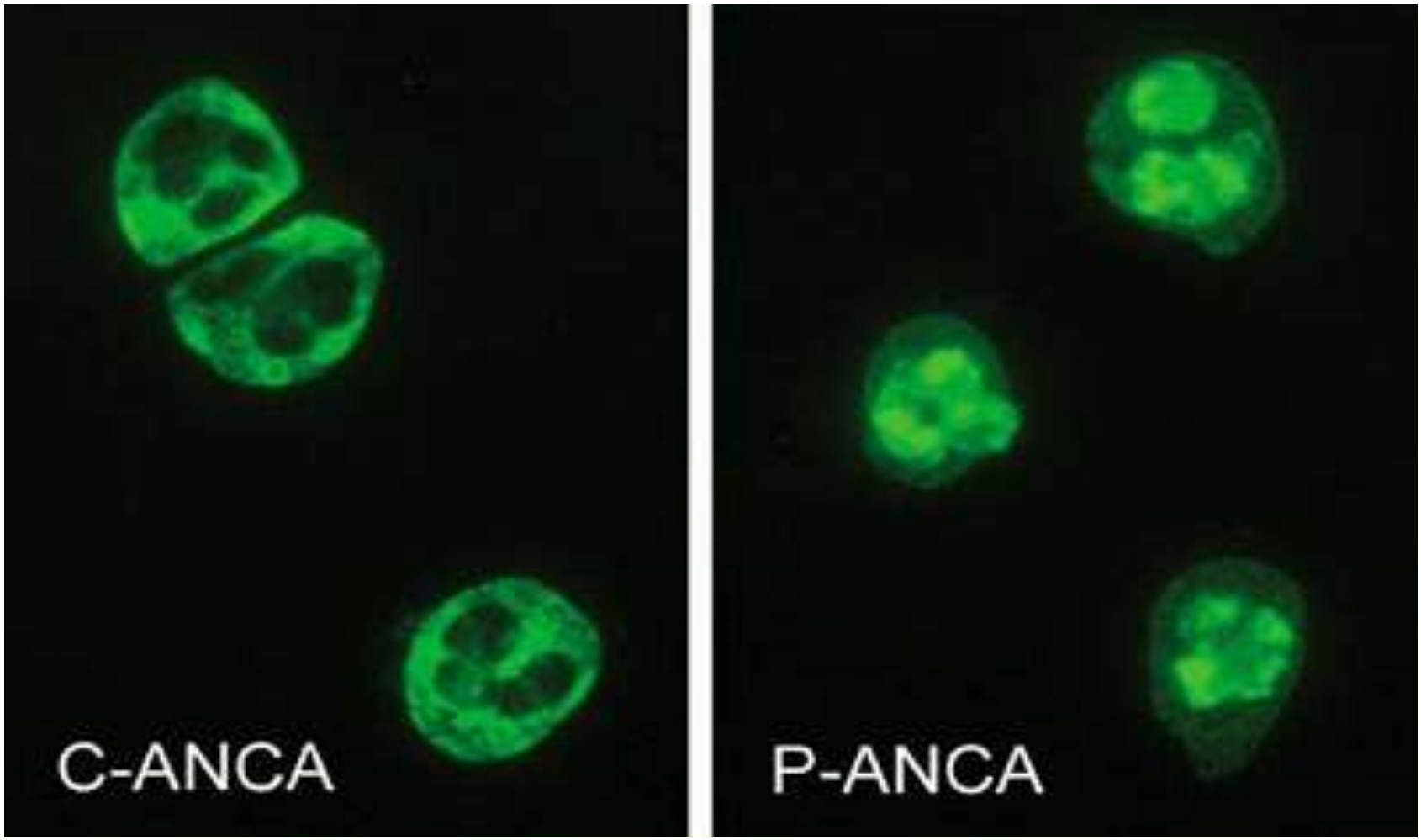
Pathogenesis

Immunological process (The leading hypothesis):

- ANCAs (autoantibody) react with cytoplasmic autoantigens (PR-3 and MPO) that are present at the surface of cytokine-stimulated leukocytes, causing the leukocytes to adhere to vessel walls, degranulate, and generate toxic oxygen metabolites.
- The interaction of ANCAs with neutrophils involves Fc receptor engagement.


Formalin Fixation
c-ANCA
Strong cationic proteins (e.g., MPO)
Weakly cationic or neutral proteins (e.g., PR3)
Ethanol Fixation
p-ANCA
c-ANCA
Antibodies to strong cations
Antibodies to neutral proteins of weak cations (e.g., PR3)

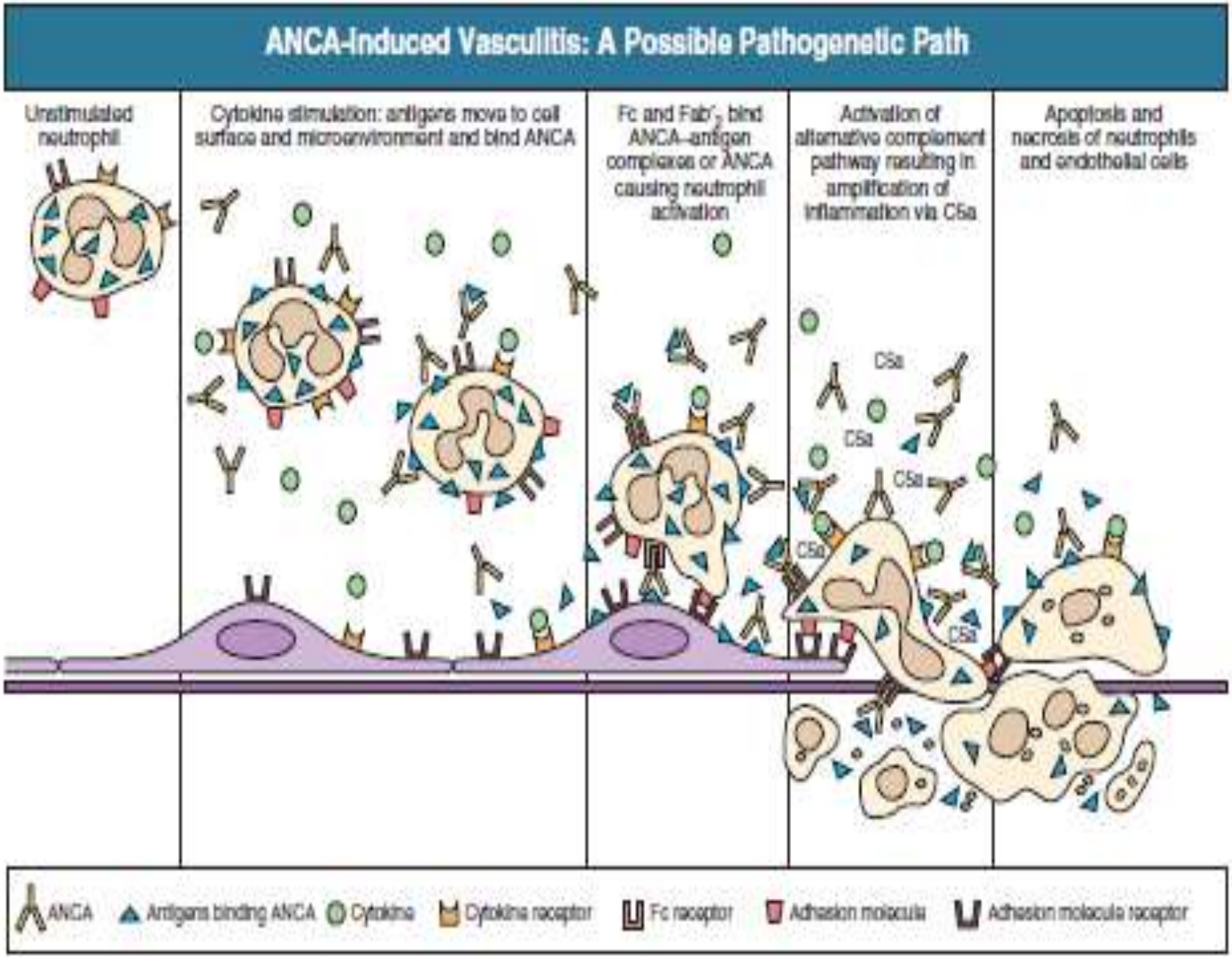
Indirect immunofluorescence microscopy showing cytoplasmic C-ANCA staining results caused by PR3-ANCA on the left and a nuclear P-ANCA staining pattern caused by MPO-ANCA on the right.



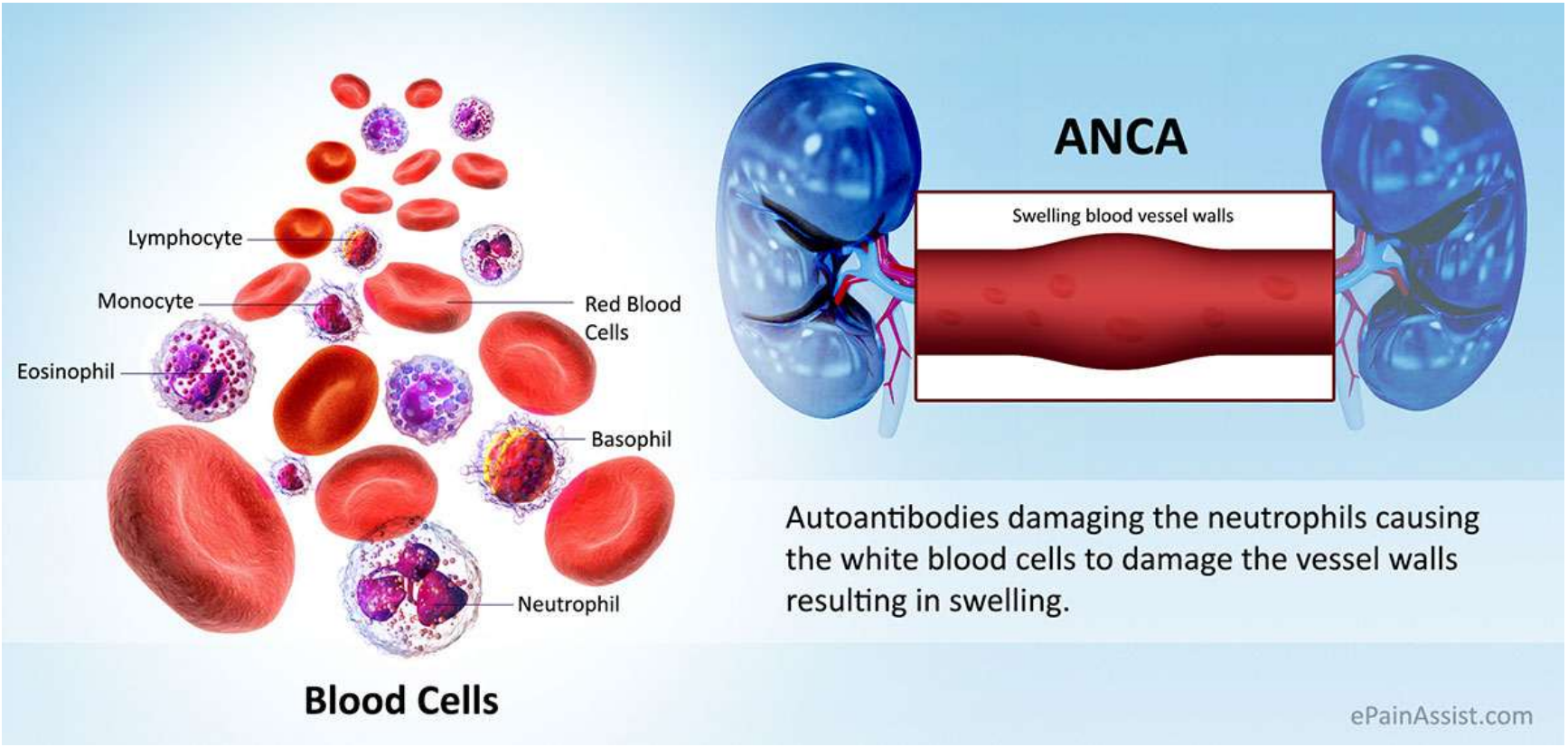
Pathogenesis

Immunological process

- Recently, autoantibodies to lysosome-associated membrane protein 2 (LAMP-2) were reported in the circulation of most patients with either MPO-ANCA or PR3-ANCA.
- LAMP-2 has homology to the bacterial adhesin FimH, and thus autoantibodies to LAMP-2 may arise by molecular mimicry secondary to infection with fimbriated gram-negative bacteria.


ANCA-Induced Vasculitis: A Possible Pathogenetic Path
Unstimulated neutrophil
Cytokine stimulation: antigens move to cell surface and microenvironment and bind ANCA
Fc and Fab'2 bind ANCA–antigen complexes or ANCA causing neutrophil activation
Activation of alternative complement pathway resulting in amplification of inflammation via C5a
Apoptosis and necrosis of neutrophils and endothelial cells
C5a
C5a
C5a
C5a
C5a
ANCA
Antigens binding ANCA
Cytokine
Cytokine receptor
Fc receptor
Adhesion molecule
Adhesion molecule receptor

Pathogenesis



Frequencies of PR3 ANCA & MPO ANCA

Table 1
Frequencies of PR3-ANCA and MPO-ANCA in ANCA-associated necrotizing vasculitic diseases

Vasculitis	PR3-ANCA (%)	MPO-ANCA (%)
Wegener's Granulomatosis	40–95	5–60[a]
Microscopic Polyangiitis	25–30	50–70
Churg-Strauss Syndrome	9–30	30–40
Renal-limited Vasculitis	25–30	50–70
Drug-induced Vasculitis[b]	10–15	80–90

[a] As reported in studies from China; Chinese WG patients mostly produce MPO-ANCA.
[b] Several other ANCA specificities can be found in drug-induced vasculitis/drug-induced lupus.

Rheum Dis Clin N Am 36 (2010) 479–489
doi:10.1016/j.rdc.2010.05.001
rheumatic.theclinics.com
0889-857X/10/$ – see front matter

Sensitivity and specificity of ANCA

- Positive results : in completely healthy individuals.
- Positive with other inflammatory renal diseases (especially lupus).
- ANCA is negative in 10% to 20% of patients with pauci-immune necrotizing vasculitis and crescentic GN .

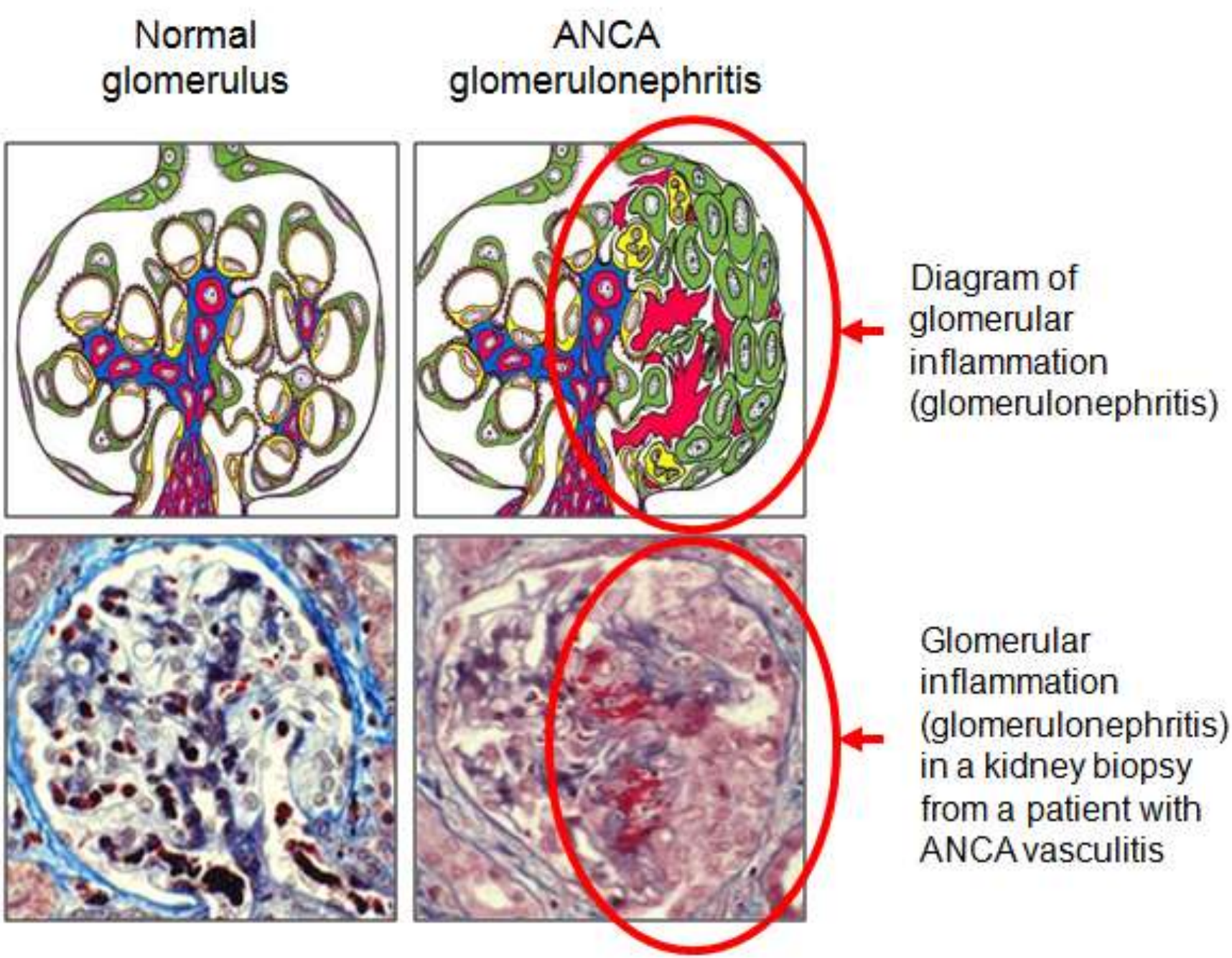
Sensitivity and specificity of ANCA

- Changes in ANCA titers over time correlate to a degree of disease activity but must be interpreted with caution.

- ANCA may be positive in inflammatory conditions other than vasculitis, including inflammatory bowel disease (IBD), rheumatoid disease, chronic inflammatory liver disease, bacterial endocarditis, and cystic fibrosis.

Renal histology

- A focal and segmental necrotizing crescentic glomerulonephritis is characteristic.
- If small vessels, e.g. interlobular arteries, are sampled, they may show inflammation and necrosis.
- Associated interstitial inflammation is often present.
- Immunostaining reveals no, or very few, immune complex or complement deposits (pauci-immune) .


Normal glomerulus
ANCA glomerulonephritis
Diagram of glomerular inflammation (glomerulonephritis)
Glomerular inflammation (glomerulonephritis) in a kidney biopsy from a patient with ANCA vasculitis

Renal histology

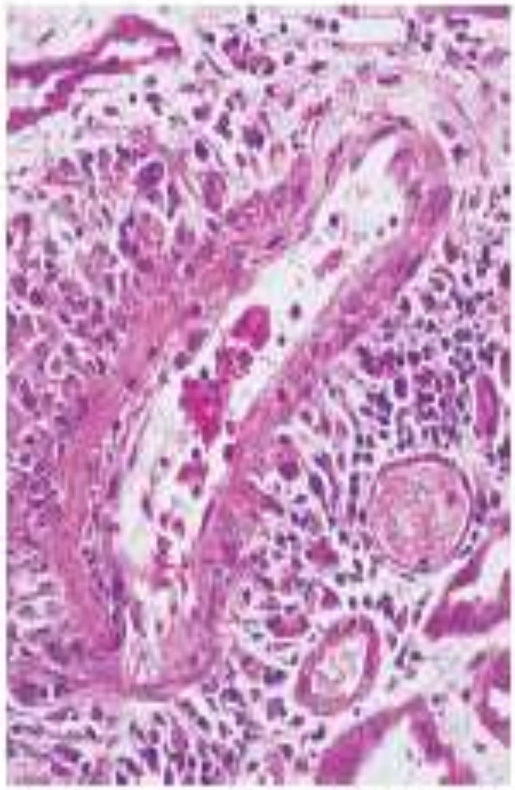
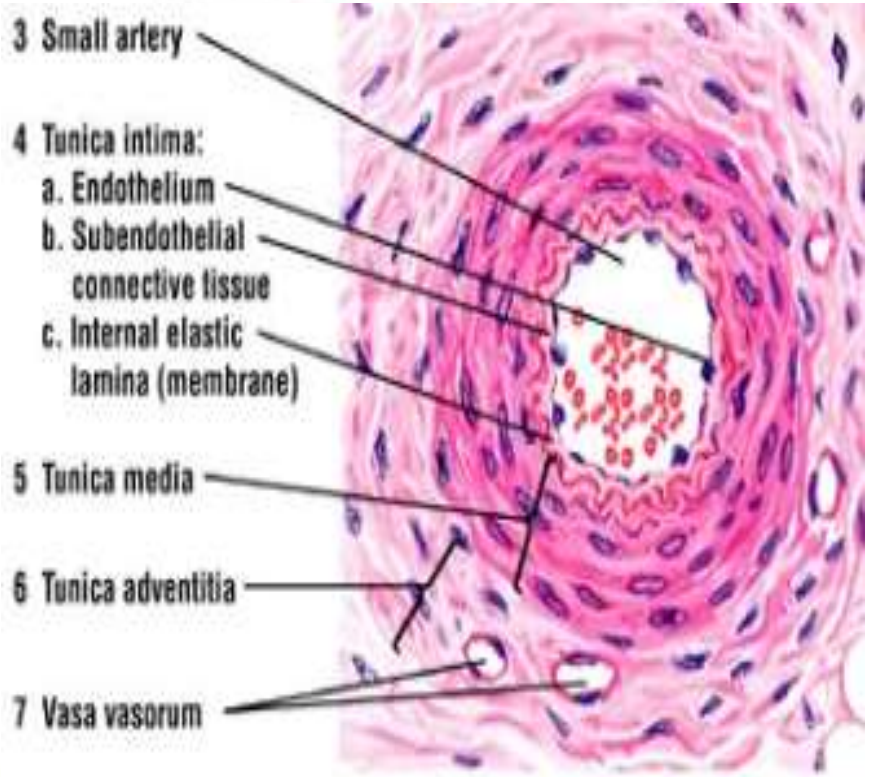


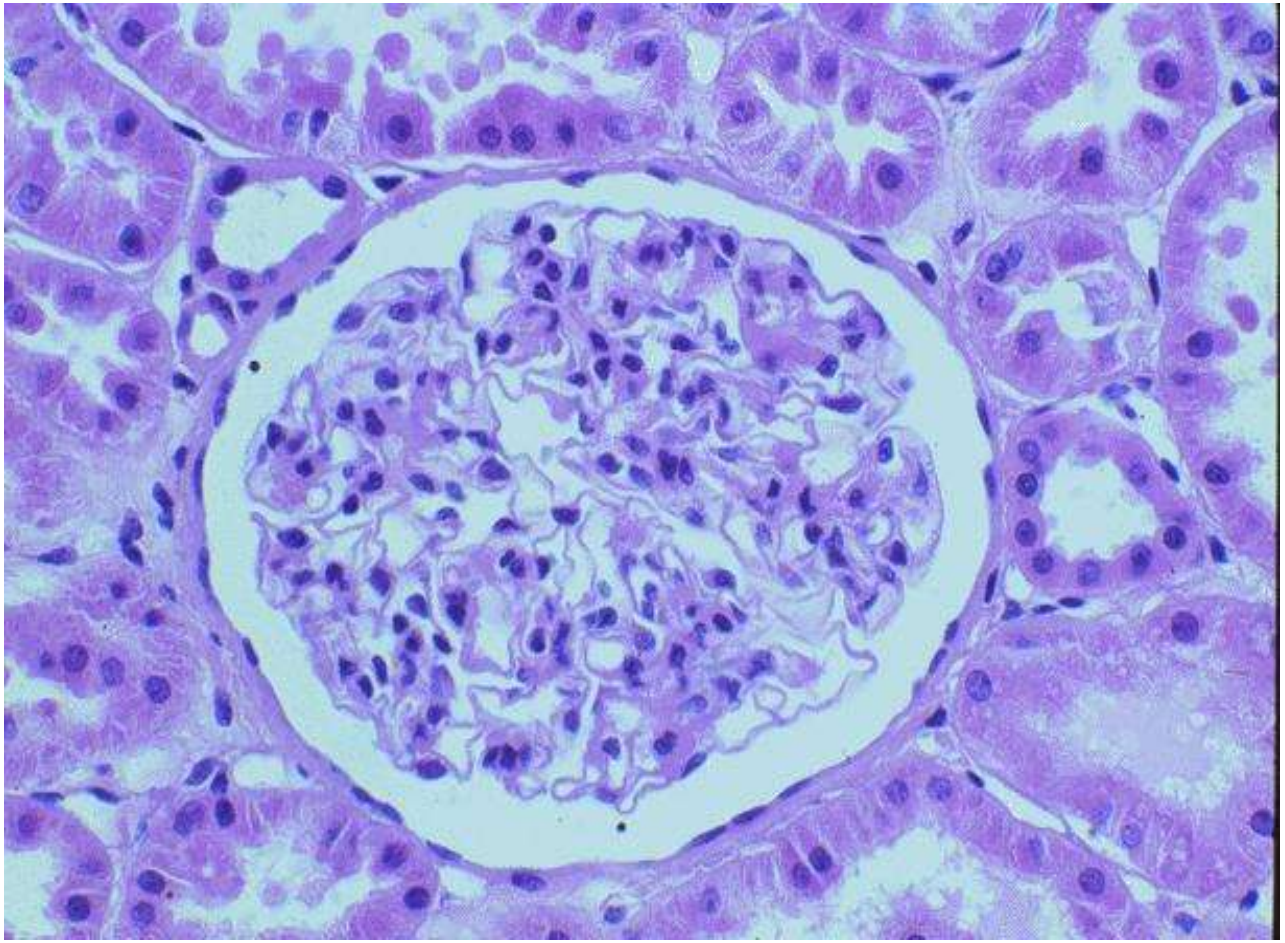
Figure 25-6 Necrotizing arteritis of interlobular artery in patient with ANCA-associated small-vessel vasculitis. There is segmental fibrinoid necrosis with adjacent perivascular leukocytic infiltration. (Hematoxylin-eosin (HE) stain; ×50.)



Normal arteriole

Renal histology

Normal glomerulus



Renal histology

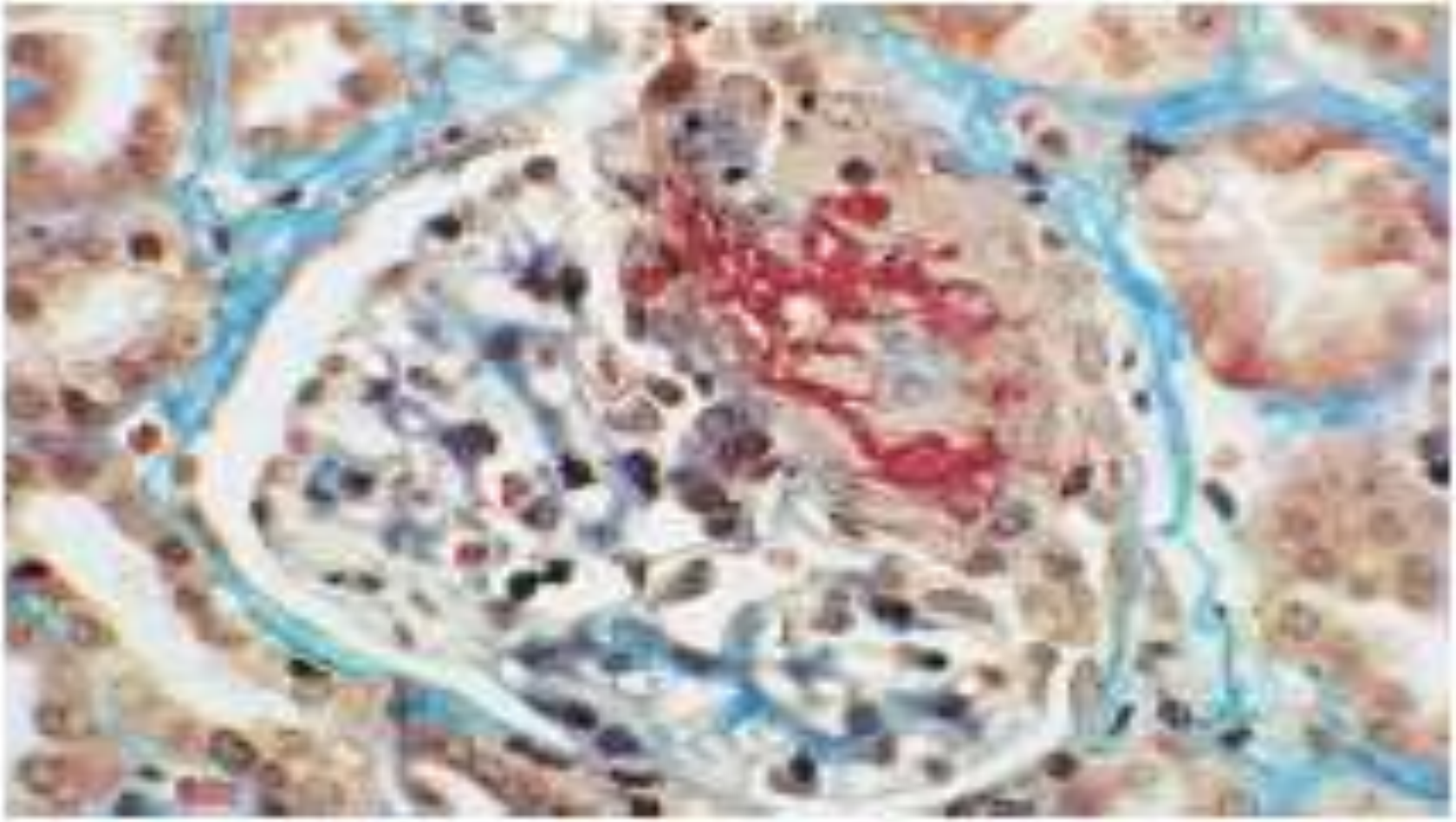


Figure 25-8 Segmental glomerular necrosis and crescent formation in patient with ANCA-associated small-vessel vasculitis. The fibrinoid material is red. The uninvolved segments appear normal. (Masson trichrome; ×150.)

Renal histology

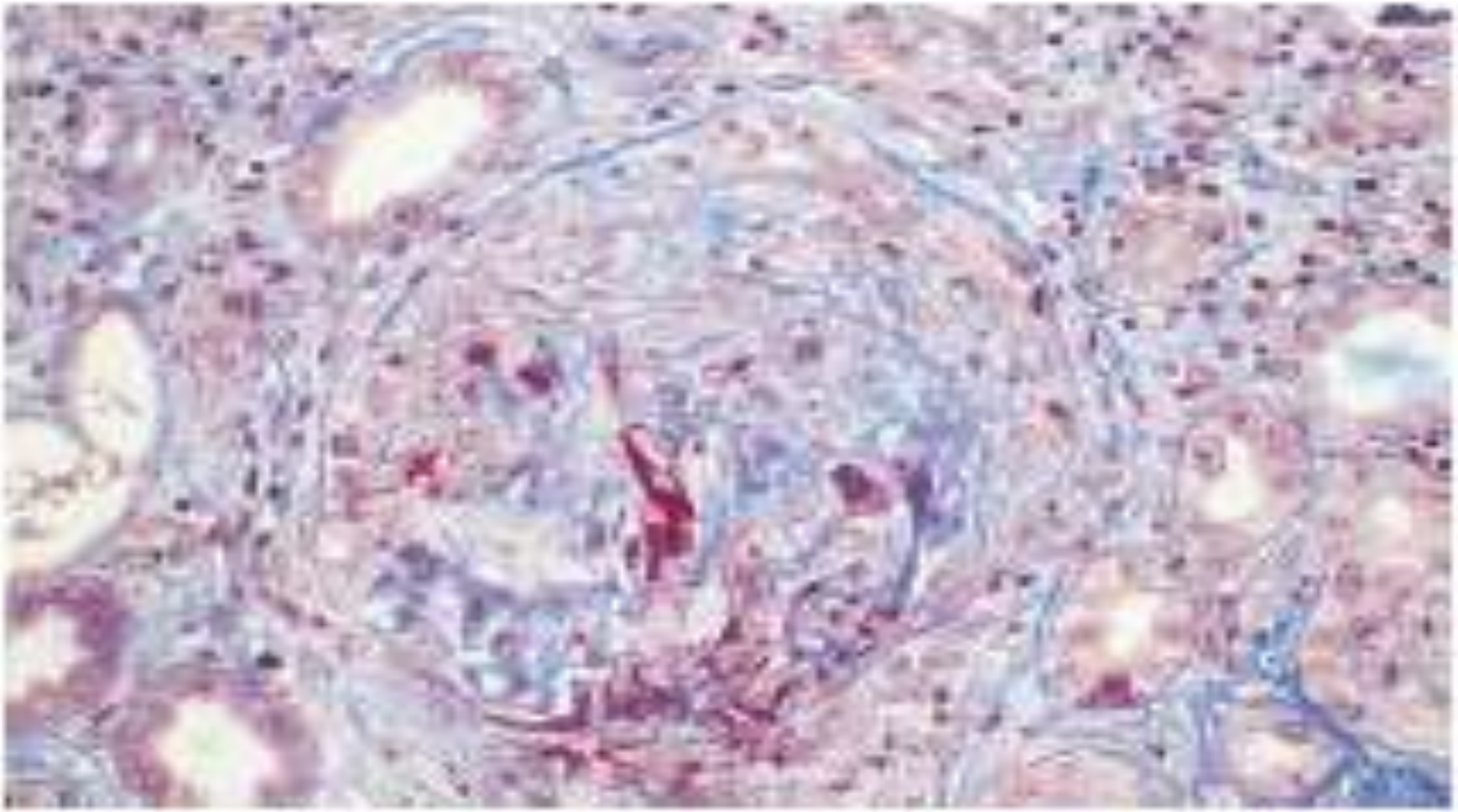


Figure 25-9 Global glomerular necrosis and circumferential crescent formation in a glomerulus from patient with ANCA-associated small-vessel vasculitis. (Masson trichrome; ×150.)

Renal histology

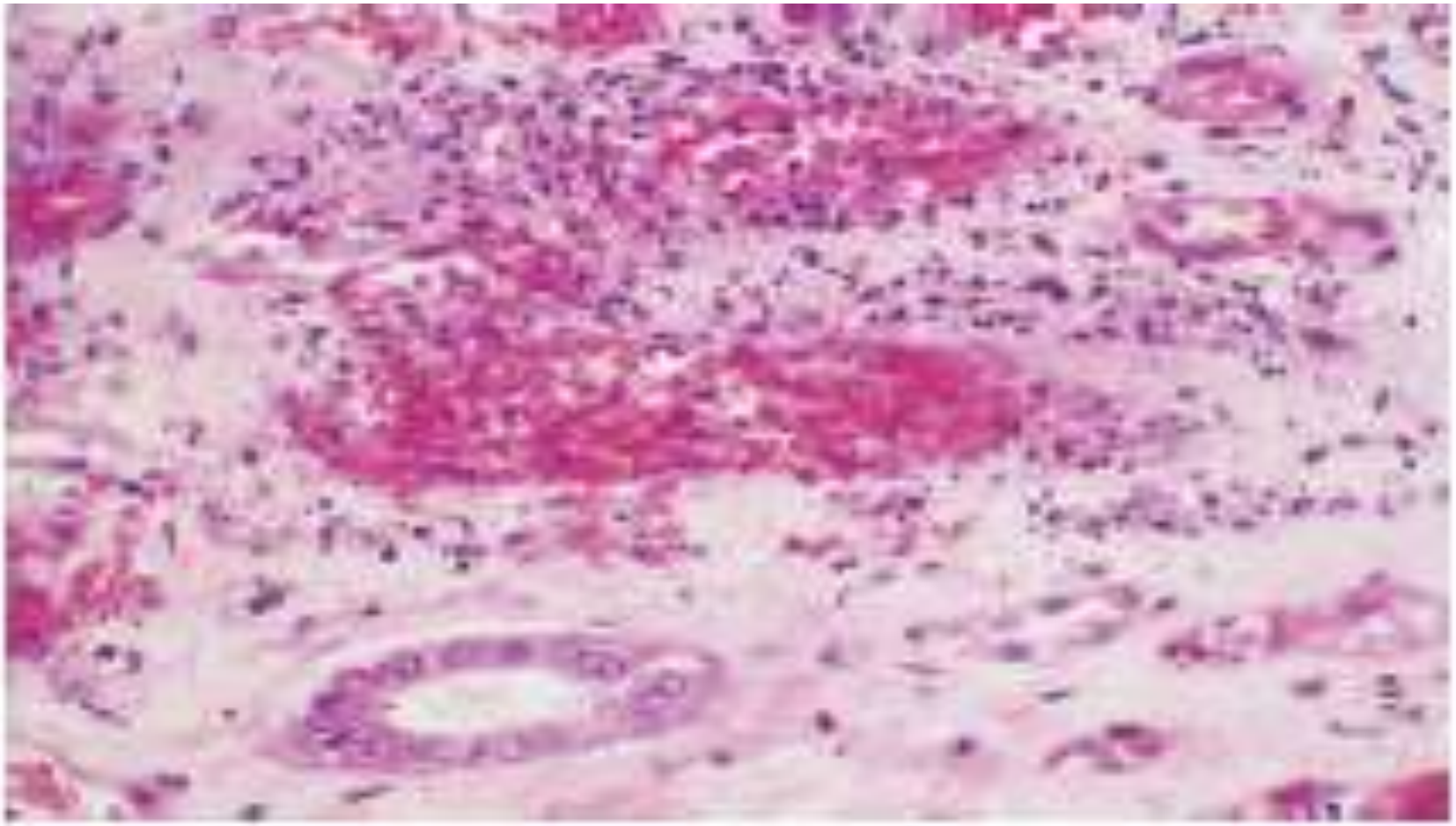
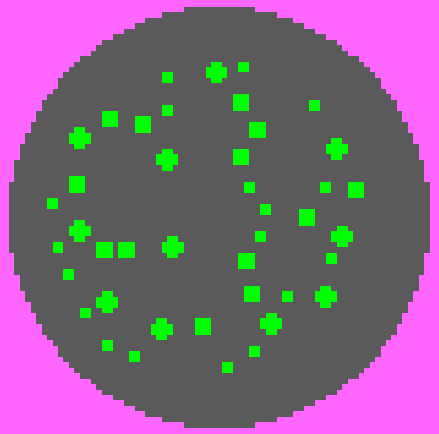


Figure 25-10 Medullary leukocytoclastic angiitis involving vasa recta in patient with granulomatosis with polyangiitis. (HE stain; ×150.)

Rapidly-Progressive Glomerulonephritis Etiologies

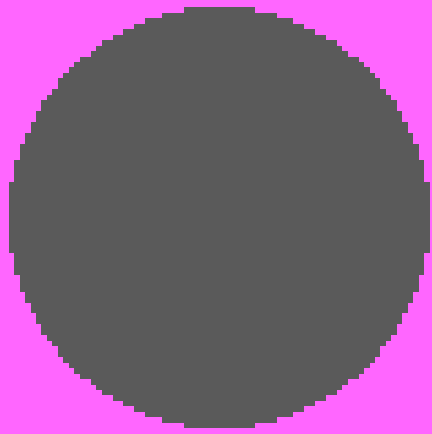
RPGN I: Anti-GBM disease

Goodpasture's, etc.



RPGN II: Immune complex diseas

Post-strep, very bad lupus, etc., etc.



RPGN III: Vasculitis

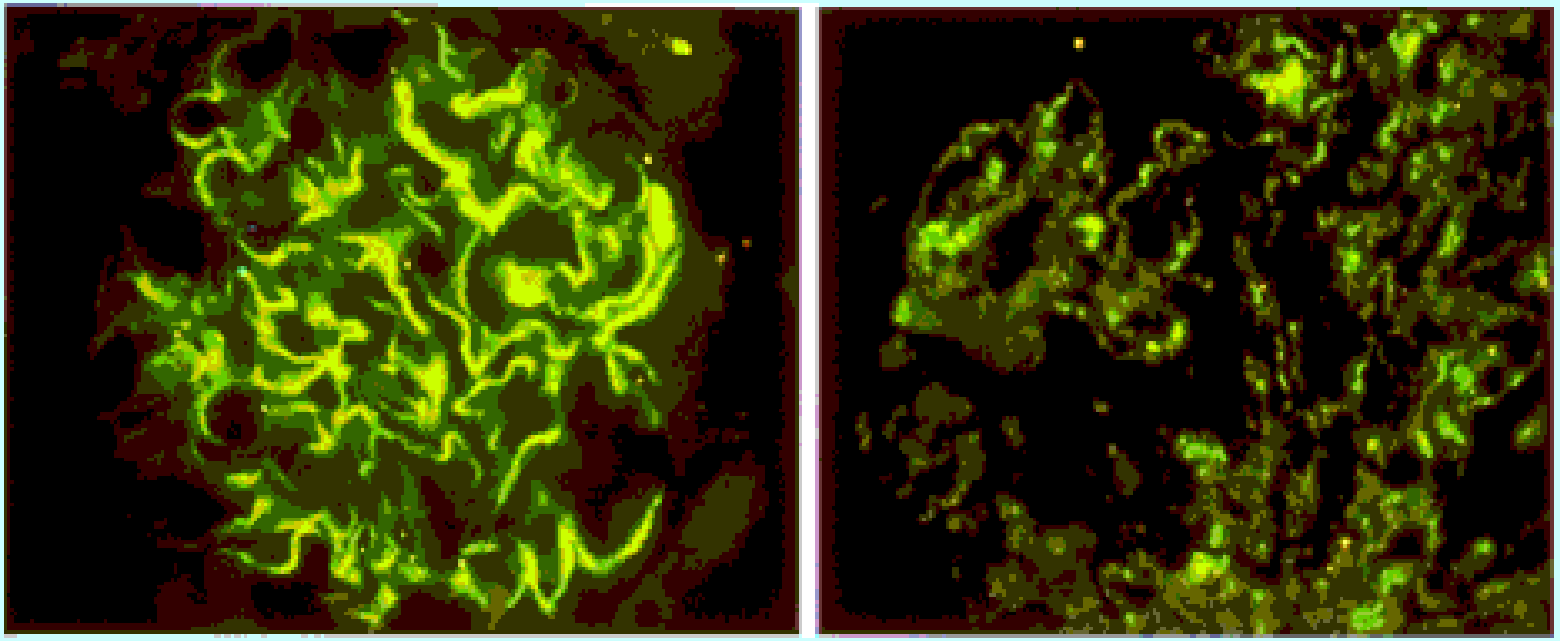
Wegener's, polyarteritis nodosa

Look for segmental necrosis

Patterns of IgG Deposition in Glomeruli

Linear

Granular



Anti-GBM

Immune Complex

Clinical Picture

Name	Definition
Small vessel vasculitis (SVV)	Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium arteries and veins may be affected.

FIG. 1. Pathogenesis of necrotizing vasculitis.

TABLE 1
Clinical Evidence for ANCA Pathogenicity

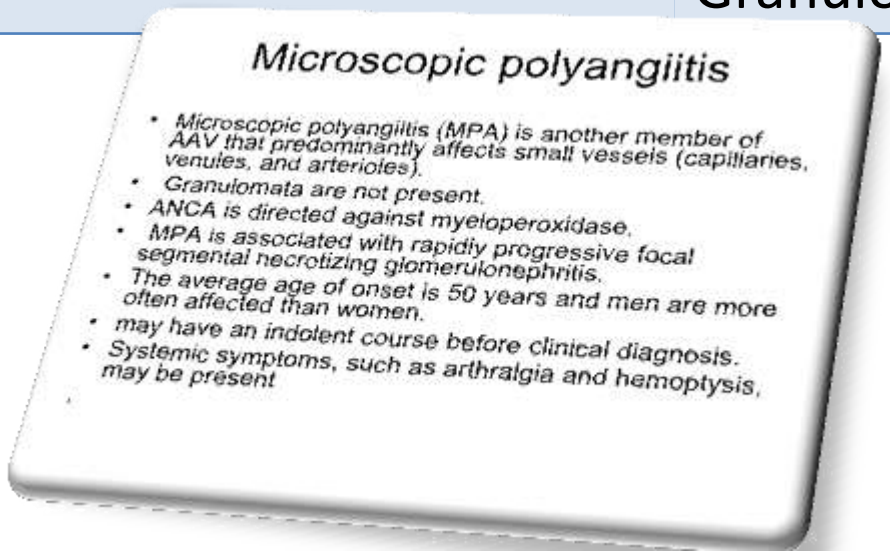
- ANCA are associated with necrotizing glomerulonephritis and vasculitis
- ANCA disease responds to immunosuppressive treatment
- ANCA titers correlate with disease activity
- There is no immunohistopathologic or serologic evidence for anti-GBM or immune complex mediation of pauci-immune ANCA glomerulonephritis or vasculitis
- Drug-induced ANCA are associated with pauci-immune necrotizing glomerulonephritis and vasculitis that disappear with discontinuation of the drug

Clinical Picture

Name	Definition
ANCA-associated vasculitis (AAV)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCAnegative.

Clinical Picture

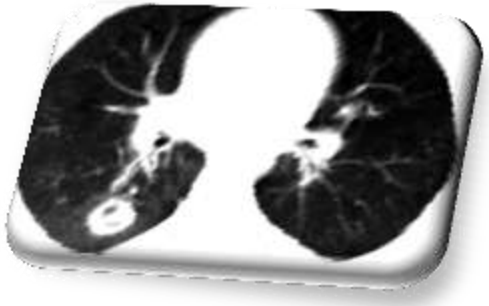
Name	Definition
Microscopic polyangiitis (MPA) P-ANCA (anti-MPO) (Confirmed as anti-myeloperoxidase)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.



Clinical Picture

Name	Definition
Granulomatosis with polyangiitis (Wegener's) (GPA) C-ANCA (anti-PR3) (confirmed as anti-proteinase 3)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.


Collapse in the bride of the nose caused by granulomatosis with polyangiitis (Wegener's). Note the hearing aid required for hearing loss due to concurrent middle ear disease

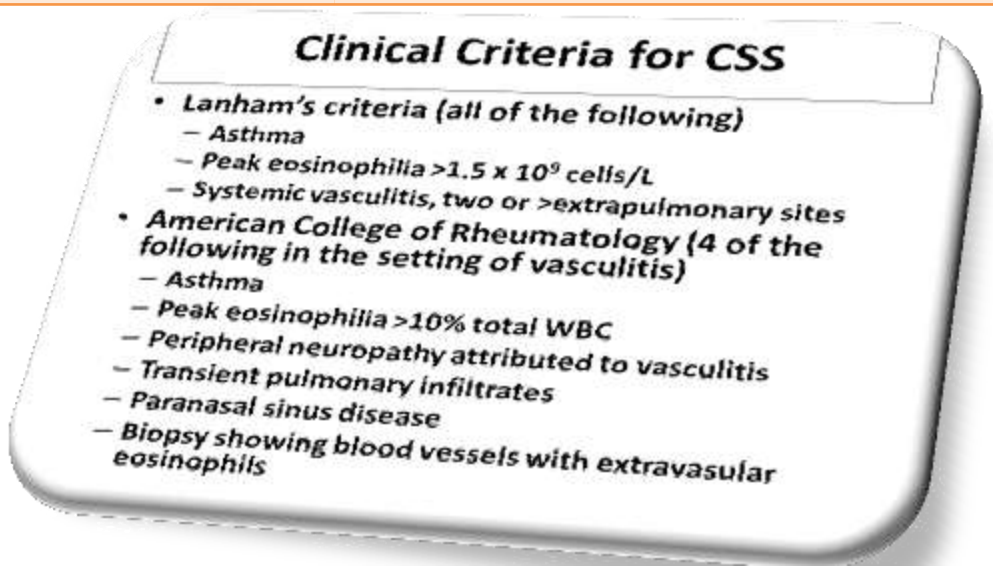



ure 16 - Radiological aspect of alveolar

Clinical Picture

Name	Definition
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.

P-ANCA (anti-MPO)
(Confirmed as anti-myeloperoxidase)



Differential diagnosis

- *Distinguish GPA, MPA, EGPA and RLV.*
- *Other causes of small vessel vasculitis*
- *Exclude* **vasculitis mimickers:** *infection (TB, endocarditis), malignancy*

Vasculitis:definitions

	PAN	MPA	WG	CSS
Systemic symptoms	+	+	+	+
ANCA	-	+	+	+
Necrotising granuloma	-	-	+	+
Asthma and eosinophillia	-	-	-	+

	Granulomatosis with polyangiitis (GPA)	Microscopic polyangiitis	Eosinophilic GPA
Ear, nose, throat	Necrotizing, destructive	–	Allergic
Lung	Nodule, cavity, infiltrate	Infiltrates	Asthma, infiltrates, nodule
Kidney	++++	++++	+ – ++
Nerve	++	+++	++++
Skin	++	+++	+++
Heart	+	+	++ (mortality)
Granuloma	++++	–	++++
Eosinophils	–	–	++++
ANCA	80%–95% PR3 5%–20% MPO 0%–20% ANCA (–)	40%–80% MPO 35% PR3 0%–20% ANCA (–)	40% MPO 35% PR3 Up to 60% ANCA (–)

Organ System Involvement in Small-Vessel Vasculitis

	Frequency of Involvement (%)				
Organ System	Microscopic Polyangiitis	GPA (Wegener)	EGPA (Churg-Strauss)	IgA Vasculitis (HSP)	Cryoglobulinemic Vasculitis
Kidney	90	80	45	50	55
Skin/cutaneous	40	40	50	90	90
Lungs	50	90	90	<5	<5
Ear, nose, throat	35	90	50	<5	<5
Musculoskeletal	60	60	50	75	70
Neurologic	30	50	60	10	40
Gastrointestinal	50	50	70	60	30

Differential Diagnostic Features of Selected Forms of Small-Vessel Vasculitis

Features	Microscopic Polyangiitis	Wegener's Granulomatosis	Churg-Strauss Syndrome	Henoch-Schönlein Purpura (HSP)	Cryoglobulinemic Vasculitis
Vasculitic signs and symptoms*	+	+	+	+	+
IgA-dominant immune deposits	–	–	–	+	–
Cryoglobulins in blood and vessels	–	–	–	–	+
Antineutrophil cytoplasmic antibodies (ANCA) in blood	+	+	+	–	–
Necrotizing granulomas	–	+	+	–	–
Asthma and eosinophilia	–	–	+	–	–

Figure 24.14 Differential diagnostic features of selected forms of small-vessel vasculitis. *All these vessel vasculitides can manifest any the shared features of small-vessel vasculitides, such as nephritis, purpura, abdominal pain, peripheral neuropathy, myalgias, and arthralgias. Each distinguished by the presence and, just as important, by the absence of certain specific features. *(Modified from reference 2.)*

Treatment

Plane of treatment include

- Active ttt: induction of remission, maintenance of remission, and ttt of relapse
- Treatment of relapse and resistant cases
- Renal replacement therapy (RRT).
- Supportive therapy
- Correction of complication

Treatment

Induction

13.1: Initial treatment of pauci-immune focal and segmental necrotizing GN

13.1.1: We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)

13.1.2: We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

Table 30 | Recommended treatment regimens for ANCA vasculitis with GN

Agent	Route	Initial dose
Cyclophosphamide[a]	i.v.	0.75 g/m^2 q 3-4 weeks. Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3.
Cyclophosphamide[b]	p.o.	1.5–2 mg/kg/d, reduce if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust the daily dose to keep leucocyte count >3000/mm^3.
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3-4 months.
Rituximab[c]	i.v.	375 mg/m^2 weekly × 4.
Plasmapheresis[d]		60 ml/kg volume replacement. *Vasculitis*: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. *Vasculitis in association with anti-GBM antibodies*: Daily for 14 days or until anti-GBM antibodies are undetectable.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; i.v., intravenous; p.o., orally.

Treatment

Maintenance

13.3: Maintenance therapy

13.3.1: We recommend maintenance therapy in patients who have achieved remission. (*1B*)

13.3.2: We suggest continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (*2D*)

13.3.3: We recommend no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (*1C*)

Treatment

13.4: Choice of agent for maintenance therapy

13.4.1: We **recommend** azathioprine 1-2 mg/kg/d orally as maintenance therapy. (*1B*)

13.4.2: We **suggest** that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. (*2C*)

13.4.3: We **suggest** trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (*2B*)

13.4.4: We **suggest** methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2. (*1C*)

13.4.5: We **recommend not using** etanercept as adjunctive therapy. (*1A*)

Treatment

Relapse

13.5: Treatment of relapse

13.5.1: We **recommend** treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see Section 13.1). (*1C*)

13.5.2: We **suggest** treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

Treatment

Relapse

Box 5 Characteristics of a flare

Flare: Recurrence, deterioration, or new onset of symptoms and signs attributable to active vasculitis

Major flare: Recurrence, deterioration, or new onset of at least one item on the Birmingham vasculitis activity score,[45-47] indicating a threat to vital organ function as a result of active vasculitis. Examples include:

30% increase of creatinine or 25% decrease of glomerular filtration rate within three months

Evidence of severe pulmonary haemorrhage or granulomata

Threatened vision (including orbital granuloma and retinal vasculitis)

Sensorineural deafness

New multifocal neurological lesions or mononeuritis multiplex

Gastrointestinal haemorrhage or perforation

Minor flare: Recurrence, deterioration, or new onset of at least three other items on the Birmingham vasculitis activity score related to non-vital organs attributable to active vasculitis. Examples include:

Epistaxis, nasal crusting, lesions on nasal endoscopy

Conductive deafness

Deafness

Rash

Myalgia, arthralgia, arthritis

(Epi)scleritis

Pulmonary symptoms not characteristic of a major relapse

Treatment

Resistant disease

13.6: Treatment of resistant disease

13.6.1: In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, we recommend the addition of rituximab (*1C*), and suggest i.v. immunoglobulin (*2C*) or plasmapheresis (*2D*) as alternatives.

13.7: Monitoring

13.7.1: We suggest not changing immunosuppression based on changes in ANCA titer alone. (*2D*)

Treatment

Renal replacement therapy

AKI :

IHD or CRRT apply during the treatment of vasculitis .

ESRD

Transplantation :

It is generally recommended that patients wait for 6 – 12 months post-remission prior to transplantation.

Ongoing ANCA positivity per se is not significantly associated with reduced graft survival.

Recurrent disease can be expected in 15 – 20% but causes graft loss in a minority.

Rejection rates are similar to the general transplant population.

Infection risk increases , presumably reflecting cumulative immune suppression.

Prognosis

- Prognosis for untreated Wegener's - 90% mortality within 2 years.
- Long-lasting remissions can be induced with cytotoxic agents particularly cyclophosphamide in conjunction with corticosteroids.
- 85-90% of patients respond to cyclophosphamide with 75% experiencing complete remission median time to remission is 12 months.
- 30 - 50% of responders with have at least one relapse.

Prognosis

- Prednisolone alone has a lower remission rate when compared to prednisolone + cyclophosphamide (56 vs. 85%), a higher relapse rate and a higher mortality with the cyclophosphamide-prednisolone combination renal and patient survival is over 75%
- Response to therapy and clinical course are similar in P-ANCA and C-ANCA disease.
- C-ANCA positive patients are more likely to relapse.

Prognosis

- With adequate immunosuppressive therapy, 5-year renal and patient survival is 65% to 75%.

- The success of long-term maintenance of renal function is inversely correlated with the serum creatinine concentration when therapy begins

Prognosis

- Adverse events from therapy, including infections, are the leading cause of death in the year following diagnosis.
- Older age, higher serum creatinine concentration at presentation, pulmonary hemorrhage, and especially dialysis-dependent renal failure correlate with an overall poor outcome.

Prognosis

- Pathologic features that correlate with renal outcome include histologically normal glomeruli, glomerular sclerosis, interstitial leukocyte infiltration, tubular necrosis, and tubular atrophy.

- Increased numbers of histologically normal glomeruli or glomeruli with cellular crescents correlated with a better prognosis than higher proportions of globally sclerotic glomeruli, suggesting that active inflammatory lesions may be suppressed if not reversed by treatment, whereas chronic injury at initiation of treatment may be irreversible.

Prognosis

- Relapse of ANCA small vessel vasculitis occur up to 40%

- Pauce-immune necrotizing GN may recur after renal transplantation.

Newer Therapeutic Agents

Principle	Mechanism	Agent	Evidence
Depletion of effector T cells	Antibodies directed against CD25 deplete activated T cells	Basiliximab Daclizumab	Experimental + clinical evidence (RA+Tx) Ongoing RCT in AAV
Regulation of effector T cells	Blockade of CD28/CD80 dependent T cell activation	Abatacept, Belatacept (both CTLA-4 fusion proteins)	Experimental + clinical evidence (RA+Tx) Ongoing trial in AAV
Block adhesion of neutrophils	Blockade of CD11b/ICAM-1 mediated adhesion to endothelium		Experimental evidence
Limit activation/ recruitment of neutrophils	Inhibition of C5 cleavage. Blockade of C5a receptor on neutrophils	Eculizumab, Pexelizumab (both anti-C5)	Experimental evidence
Enhance vascular repair	Promote EPC mobilization and function	EPO Statins	Experimental + clinical evidence
Inhibition of migration	Blockade of a4-integrins on T cells	Natalizumab	Experimental + clinical evidence in MS
Interfere with granuloma formation	Blockade of TNF-α	Infliximab Adalimumab	Experimental + clinical evidence in AAV
Depletion of B cells	B-cell depletion by antibodies recognizing CD20/CD22	Rituximab, Epratuzumab (both anti-CD20)	Experimental + clinical evidence in AAV
Inhibition of B-cell maturation	Neutralization of BLys. Blockade of BLys-receptors on B cells	Belimumab (anti-BLys) Atacicept (anti-TACI)	Experimental evidence
Anti-microbial treatment	Reduction of microbial flora that might trigger disease flares	Cotrimoxazol	Experimental + clinical evidence in AAV


خزعبلات